



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

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Date: NOV 19 2003
From: Consumer Safety Officer, Division of Dietary Supplement Programs, Office of
Nutritional Products, Labeling and Dietary Supplements, HFS-810
Subject: 75-Day Premarket Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

Subject of the Notification: NK Activator
Firm: MicroBio Co., LTD
Date Received by FDA: Feb 21, 2003
90-Day Date: May 24, 2003

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and
Cosmetic Act, the attached 75-day premarket notification and related correspondence for the
aforementioned substance should be placed on public display in docket number 95S-0316 as
soon possible since it is past the 90-day date. Thank you for your assistance.

Vicki K. Luttrell
CSD

95S-0316

RPT175



MAY 12 2003

Food and Drug Administration
College Park, MD 20740

Mr. William Lu, President
MicroBio **Co., LTD.**
81, Gauyang N Road
Lungtan Shiang, Taoyuan Hsian, Taiwan

Dear Mr. Lu:

Please refer to your 75 day New Dietary Ingredient (NDI) Notification dated February 18, 2003, received and filed on February 21, 2003, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413 of the Federal Food, Drug, and Cosmetic Act (the Act)) and 21 CFR 190.6). Your notification notified FDA of **your** intent to market NK Activator, a product containing **MS-20**, a substance that you **assert** is a new dietary ingredient.

Your notification states that, under the recommended serving and conditions of use, take once a day before a meal, either a capsule, tablet or soluble powder (dissolved in 100ml of water) formulation of **MS-20**, and that the daily serving should not exceed **5 grams** per person per day. **You** state that "NK Activator" is said to have the following properties: enhancement of "nature" [sic] killer cell activities, growth inhibition and induction of apoptosis of MCF7 breast cell, and inhibition of 15-lipoxygenase. The primary use of the product is for enhancement of "nature" [sic] killer cell activities.

Under 21 **U.S.C. 350b(a)(2)**, the manufacturer or distributor of a dietary supplement that contains **a** new dietary ingredient that has not been present in **the** food supply **as an** article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews **this** information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If **this** requirement is not met, the dietary supplement is deemed to be adulterated under 21 **U.S.C. 342(f)(1)(B)** because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable **risk** of illness or injury.

The notification contains conflicting information concerning the description of the dietary supplement that contains the new dietary ingredient. You indicated that three types of formulations are to be manufactured **as** dietary supplements: capsule, tablet, and soluble powder. Each unit (gram) of the dietary supplement contains one milliliter of MS-20 spray dried. At a later point on the same page, you stated that there are two formulations of the product. Capsules of the product are said to contain 500 **mg** of the “proprietary fermented soybean extracts.” The soluble powder form of the product is said to contain 1.5 g of the “proprietary fermented soybean extracts.” You did not provide information in the notification about specifications and controls that were used for the three production batches.

In addition, the notification did not provide information about the composition of the test article **MS-20**. Without this information no determination can be made about potentially active ingredients and/or their concentrations. It is unclear how the test articles are qualitatively/quantitatively related to the proposed dietary supplement.

The information in the notification to provide a history of use for your products states the “similar products using the same strains of beneficial microorganisms and culture conditions were produced in smaller scale and were sold in Japanese market though direct sales to hospitals for more than 50 years **as** a nutrient supplement.” No adverse effects are said to have been reported. There is no information **as** to the composition of these “similar products” and no information is included that actually documents their use.

In conclusion, the FDA has carefully considered your notification for the new dietary ingredient MS-20 and the dietary supplement NK-Activator and the information does not provide evidence supporting the safe use of the ingredient or the supplement containing it. With respect to the ingredient tested, the protocols state, “The components are very complicated. Until now, its effective components are still unable to determine.” The notification does not provide information regarding the composition of the final ingredient MS-20. It is not possible to determine what are likely to be the active components from the limited information submitted. Similarly, it is not possible to determine to what degree of concentration of potentially active ingredients may have occurred during the manufacturing process. Without this information, it is not possible to determine whether appropriate end points were included in the studies that were reported. Therefore, no safety conclusions can be drawn from the information presented.

For the reasons discussed above, the information in your submission does not provide **an** adequate basis to conclude that MS-20, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such **an** ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Page 3 – Mr. William Lu, President

Your notification will be kept confidential for 90 days after the filing date of February 21, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

Please contact Victoria Lutwak at (301) 436-2375 if you have questions concerning this matter.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Susan J. Walker M.D.", with the letters "FDR" written in smaller capital letters below the signature.

Susan J. Walker, M.D.

Acting Director

Division of Dietary Supplement Programs

Office of Nutritional Products, Labeling

and Dietary Supplements

Center for Food Safety

and Applied Nutrition

Enclosure

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplement (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD20740

February 18, 2003

Dear Sir:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, MicroBio Co., LTD located at Taoyuan, Taiwan submits this notification to FDA for MS-20 as a new dietary ingredient and "NK activator" as a dietary supplement product.

Accompany with this letter MicroBio Co., LTD submits an original and two copies of the notification to your office as a manufacturer who intends to market dietary supplements that contain a new dietary ingredient. This notification is filed at least 75 days before the dietary supplement "NK Activator" contains new dietary ingredient MS-20 will be introduced or delivered for introduction into interstate commerce. We believe we have sufficient information on hand to conclude that dietary supplement product "NK Activator" containing new dietary ingredient MS-20 meets food grade specifications and manufactured in accordance with current good manufacturing practices. We also believe the scientific data and information demonstrating MS-20 when used under the conditions suggested in the labeling would not present a significant or unreasonable risk of illness or injury, and would reasonable be expected to be safe.

Please do not hesitate to contact us if you have questions or concerns about the information contained in the notification.

Sincerely

Billy J. Chou, DVM, Ph.D., DABT



Chief, Research and Development Center
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New Dietary Ingredient Notification
for MS-20

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MICROBIO

I. The Manufacturer

Mr. William Lu, President
MicroBio Co., LTD
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Lungtan Shiang, Taoyuan Hsian, TAIWAN
Tel: 886-3-471-6886
Fax: 886-3-471-0288

II. MS-20, the New Dietary Ingredient

MS-20 is a proprietary symbiotic fermented soy extract that manufactured in a GMP facility at MicroBio Co., LTD. This facility is also certified by ISO9001 as a bulk pharmaceutical material production plant.

The soymilk is fermented with beneficial lactic acid bacteria and yeasts. The microorganisms used in the fermentation processes are generally regarded as safe that include but not limit to *Lactobacillus paracasei*, *Lactobacillus burglarius*, *Saccharomyces cerivisiae*, etc. These microorganisms are often found as intestinal micro flora and in some traditional fermentation products. MS-20 is pathogen free with following physical characteristics: specific gravity at 1.136gm/ml with 71.49% moisture, 17.6% carbohydrate, 5.45% of crude protein, 5.15% ash, 0.16% crude fat, and 0.15% crude fiber. Besides the major compositions, it also consists several vitamins and minerals.

The product specifications and chemistry, manufacturing, and controls were established by using three production batches. Genistein and daidzein contents, HPLC fingerprints, pH values, as well as other physical properties (odors, appearances, colors, clarity, tastes, and precipitates, etc) were used to establish the specifications. Biological activities were established by antibacterial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and Methicillin resistant *Staphylococcus aureus* and 15-lipoxygenase inhibition activities. More than 10 acceptable production batches were produced since the establishment of the specifications.

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III. Dietary Supplements

A. Level of New Dietary Ingredient in the Product

Three types of formulation have been manufactured as dietary supplements at a cGMP pharmaceutical formulation plant. Each unit (gram) of the dietary supplement contains one milliliter of MS-20 spray dried. Pharmaceutical grade technical additives or processing aids were added to make capsule, tablet, and soluble powder formulations. Biological activity measurements established for the new dietary ingredient MS-20 were used as the quality control for the dietary supplements.

B. Conditions of Use of the Products Stated in the Labeling

MicroBio Co. LTD has generated sufficient experimental data in: nature killer cell activities enhancement; and growth inhibition and induction of apoptosis in MCF7 breast cells; 15-Lipoxygenase inhibition and anti-arteriosclerosis pharmacological areas. Based on the experimental results and previous human use experiences in Japan that the recommended daily doses for any of the above three pharmacological areas will not exceed 5 grams per person per day.

In this notification MicroBio Co., LTD presents information for a dietary supplement product named "NK Activator" for enhancement of nature killer cell activities.

At later date, MicroBio Co., LTD will submit other dietary supplement notification(s) for other two pharmacology areas.

C. Use and Application information

1. Description of the Product

There are two formulations for this product: a capsule will contain one milliliter of MS-20 spray dried; and a sachet of dissolvable powder drink that will contain three milliliter of MS-20 spray dried

2. Product Specifications

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Two tables side-by-side one for capsule, the other for soluble powder

Amount per serving (Capsule)		% Daily Value	Amount per serving (Soluble powder)		% Daily Value
Calories	1Kcal		Calories	3Kcal	
Total Fat	2mg	<1% *	Total Fat	6mg	<1%*
Total Carbohydrate	200mg	<1% *	Total Carbohydrate	600mg	<1% *
Total Protein	65mg	1.3%*	Total Protein	195mg	1.3%*
Total amino acids	39mg	**	Total amino acids	117mg	**
Proprietary Fermented Soybean Extracts	500mg	**	Proprietary Fermented Soybean Extracts	1.5g	**

*Percent Daily Values are based on a 2 Kcal diet

**Due not established daily value

3. How to use NK Activator

We recommend taking a product (capsule or soluble powder) once a day before meal. The soluble powder sachet should be dissolve with 100 ml of water.

4. Efficacy of NK Activator

NK Activator possesses the ability to enhance nature killer cell activity, in animals and human. It is concluded NK Activator can restore nature killer cell activity.

IV. Efficacy of NK Activator

A. Physiology of NK cells

Natural killer cells (NK cells) are lymphoid cells that participate in body immune reactions. They are large lymphocytes with properties of both lymphocytes and monocytes. Nature killer cells spontaneously kill a variety of target cells in a non-MHC restricted manner, without priming or activation. Nature killer cells circulate in the blood and spleen where they develop their granules and cytolytic activities but majority of the NK cells present in the body are in low activity state. Nature killer cells activities rise to adult values shortly after birth and are stable throughout life. Systemic NK activity is easily suppressed by a number

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of factors including surgery, cytotoxic drugs, estrogen, progesterone, stress, smoking, and many diseases, including infections, and tumors. Nature killer cells become more active and increase the cytotoxicity in response to immune regulatory proteins. Nature killer cells acquired their name from the fact that they can kill some (but not all) established lines of tumor cells; it was later discovered that these lines were sensitive to NK killing because they expressed reduced levels of MHC Class I molecules. Therefore, it is considered that NK cells are one of important members in immunological surveillance mechanism in a living body for removing tumor cells or abnormal cells under tumor progression. The primary function of NK cells is surveillance that is effective against low numbers of targets that express high tumor specific antigen (TSA) epitope densities, and low MHC expression augmented lyses. Nature killer deficient animals have increased incidence of malignant disease. Depletion of NK increases the severity of disease. Boosting of NK decreases the severity of disease. Transfusion with enriched NK or LAK (lymphokine activated killer) cells decrease severity of the disease.

B. Animal Study of MS-20

Sixty male Balb/c mice, 6 weeks old, were used to investigate the immune modulation activity of NK Activator. They were fed with 20ml/kg of PBS buffer, 0.1%, or 0.4% NK Activator daily for 3 weeks, and then were sacrificed to obtain the blood samples and spleens for specific and non-specific immunity study.

The results of non-specific immunity have shown there was no significant difference in the ratios of spleen and body weights among the group of Balb/c mice fed with 0.1%, 0.4% NK Activator, and PBS buffer (Table 1).

Table 1. Ratios of spleen and body weights of the mice fed with PBS buffer or NK Activator

Group	Number	Spleen /Body Weight (mg/g)	p value
PBS buffer	10	4.24±0.41	
0.1% NK Activator	10	4.69±0.55	0.067
0.4% NK Activator	10	4.77±0.74	0.078

The p values were analyzed by one-way ANOVA test.

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The activities of NK cells among the different treated groups were also studied in this experiment. It was found the higher activity in the group of Balb/c mice fed with NK Activator than with PBS buffer (Table 2). The more NK Activator was fed the higher NK cell activity was obtained.

Table 2. NK cell activities of the mice fed with PBS buffer or NK Activator

Group	Number	NK cell activity, killing %	p value
PBS buffer	10	24.8 ± 4.8	
0.1% NK Activator	10	33.2 ± 4.2	0.0012**
0.4% NK Activator	10	35.1 ± 5.9	0.00028**

The p values were analyzed by one-way ANOVA test.

** Significant difference at 0.01 level compare with control

The amounts of IL-2 and IL-4 produced were examined by using 2 µg/ml Con A to stimulate spleen cells among the tested groups. The data were shown IL-2 production by the spleen cells of Balb/c mice fed with 0.4% NK Activator was the highest in three tested groups, but the amount of IL-4 was the lowest (Table 3). There was positive correlation with IL-2 increasing and IL-4 decreasing between higher and lower dosages. This was demonstrated that NK Activator product could stimulate Th 1 immune response rather than Th 2.

Table 3. Serum IL-2/IL-4 of the mice fed with PBS buffer, 0.1% or 0.4% NK Activator

Group	Number	IL-2	p value	IL-4	p value	IL-2/IL-4
PBS buffer	10	144.1 ± 23.5		30.4 ± 6.2		4.7
0.1% NK Activator	10	236.3 ± 40.5	8.2*10 ⁻⁶ **	22.8 ± 4.5	0.012**	10.4
0.4% NK Activator	10	251.3 ± 35.4	2.9*10 ⁻⁷ **	14.3 ± 5.5	1.6*10 ⁻⁵ **	17.6

The p values were analyzed by one-way ANOVA test.

** Significant difference at 0.01 level compare with control

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C. Human Study of NK Activator

An 8-week, open-label, randomized, cross-over, and comparative clinical study for the evaluation of the impact of NK Activator for reducing the incidence of chemotherapy induced neutropenic fever in cancer patients was conducted. Sixteen cancer patients, with different types of malignancies including breast cancer, head and neck (H&N) cancer, gastrointestinal (GI) cancer, lymphoma and nasopharyngeal carcinoma (NPC) were undergoing chemotherapy in this study. In the healthy immuno-competent individuals, the average NK cell activity detected by us at an effector: target of 25:1 was 34.5%. The baseline NK cell activity was found to be low in all patients with the range of 0.74-10.4%. However, NK cell activity was significantly increased for the patients with oral administration of NK Activator after 4 weeks (Table 4). The percentage of NK cell activity based on the baseline in the group having NK Activator ranged from 80-492% in breast cancer patients, 71-818% in NPC patients, and 108-280% in GI cancer patients. The average augment folds of NK cell activity with NK Activator compared to without NK Activator in different cancer patients were shown in the range of 2-3 (Fig. 2). Particularly, NK cell activity was raised and reached to the normal range in many patients with NK Activator.

Table 4. The effects of NK Activator on NK cell activity in cancer patients during chemotherapy

Variable	N	NK Activator	Control	p value
NK Cell Activity %	16	12.2±9.8	5.7±3.2	0.03*

The p values were analyzed by repeated measure analysis

*Significant difference at 0.05 level compare with control

**Significant difference at 0.01 level compare with control

※ Dose: 5 ml in the morning & 3ml in the afternoon

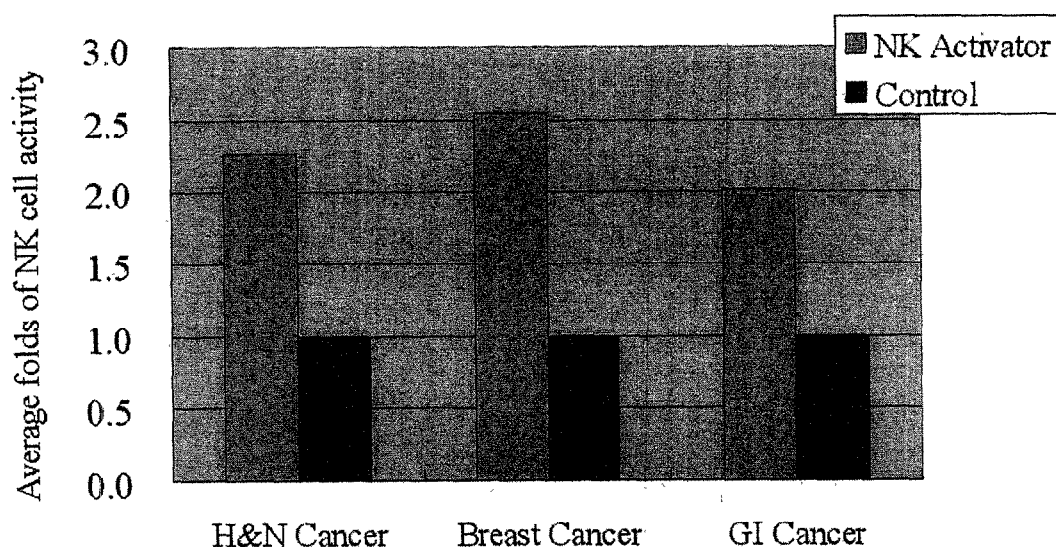


Fig. 1. The average folds of NK cell activity in cancer patients

V. Evidences of Safety

The following toxicity studies were conducted at Pre-clinical Toxicology Department of Development Center for Biotechnology (DCB), Taipei, Taiwan. These studies were performed in an AAALAC accredited animal facility and were strictly in compliance with USFDA good laboratory practice (GLP) regulations. Protocols were designed in accordance to OECD, USFDA, and ICH guidelines.

A. HPRT Gene Mutation Assay (Appendix A)

MS-20 was studied with HPRT gene mutation assay in Chinese hamster ovary cells (CHO/HPRT) in the absence and presence of Aroclor 1254-induced rat liver S9. The HPRT gene mutation assay was analyzed at 3.125, 6.25, 12.5, 25, 50, and 100 $\mu\text{l/ml}$ for test without S9 activation and 1.5625, 3.125, 6.25, 12.5, 25, and 50 $\mu\text{l/ml}$ for test with S9 activation. Allowing a period of 5 hours for phenotype expression, the treated cultures were selected for 6-TG resistant colonies. The mutation frequency was calculated based on 10^6 clonable cells. None of the test concentration with or without S9 activation showed positive response.

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B. Micronucleus Assay in Mice (Appendix B)

MS-20 was studied with Micronucleus assay in mouse peripheral blood in ICR mice. MS-20 in its undiluted form was given to 5 male mice per group by gavages at doses of 20, 10, and 5 ml/kg body weights. The positive control Mitomycin C was administered *i.p.* Blood samples were collected 48 hours after the test article administration to evaluate the presence of micronucleus in reticulocytes. The results indicated that there was no significant increases in induction of micronucleus in all MS-20 treated groups.

C. *In vitro* Chromosome Aberration Assay (Appendix C)

MS-20 was studied with chromosome aberration assay in Chinese hamster ovary cells in the absence and presence of Aroclor 1254-induced rat liver S9 to evaluate the clastogenic potential of the test article. Chromosome aberration was analyzed with three test schemes: 3-hour exposure without and with S9 activation (schemes I, II) and 20-hour continuous exposure without S9 at 100, 50, 25, 12.5 and 6.25 $\mu\text{l/ml}$. A concurrent cytotoxicity assay indicated that the top analyzable concentrations for test schemes I, II, and III were 50, 100, and 25 $\mu\text{l/ml}$ respectively. The results indicated the percents of aberrant cells of vehicle control and the three test schemes were all 0%. The MS-20 did not cause increase in the frequency of chromosome aberrations in Chinese hamster ovary cells.

D. Acute Oral Toxicity Study in Sprague-Dawley Rats (Appendix D)

An acute oral toxicity study was conducted on MS-20 in Sprague-Dawley rats by gavages. Forty-eight rats were randomly assigned into four groups of six males and six females. The undiluted MS-20 at 5, 10, and 20 ml/kg body weights (2.5, 5, and 10 ml/kg twice at two hours apart) was given to animals the first day and the animals were observed for 14 days. Results indicated that there are no observable differences in clinical signs, mortality, body weight, and gross necropsy when compare to control. Dosing levels at 20 ml/kg body weights (maximum dosing volume can reasonably given to the rats) provides 200 times margin of safety for the maximum recommended human dose of 5 ml per day per 50 kg person for the dietary supplement products.

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E. Twenty-eight Day Oral Toxicity Study in Sprague-Dawley Rat (Appendix E)

MS-20 was administered to 10/sex/group Sprague-Dawley rats orally at dose levels of 0, 1.5, 5, and 15 ml/kg body weights for 28 days. Daily observation, clinical signs, mortality, body weight and body weight gains, food consumption, ophthalmologic changes, urinalysis, hematology, serum chemistry, organ weights and organ to brain weight ratios, gross necropsy, and histopathology were evaluated and recorded. No mortality was observed in treated and control rats during study. Intermittent salivation since day 10 and thereafter were observed in rats treated at 15 ml/kg body weights. Slight and scattered but statistically significant decreases in food consumption were also noted in rats treated at 15 ml/kg body weights. There were no significant differences in mean body weights, mean body weight gains, ophthalmologic changes, urinalysis, hematology, serum chemistry, organ weights and organ to brain weight ratios, as well as gross necropsy changes between the control and MS-20 treated rats. There were no treatment related histopathological changes observed in this study. In conclusion, the results of this study suggested that daily administration up to 15 ml/kg body weights for 28 days did not cause any adverse effects in Sprague-Dawley rats. The no observable adverse effect level (NOAEL) is greater than 15 ml/kg body weights that is approximately 150 times the maximum recommended human dose for the dietary supplement products.

The following studies were conducted at MDS Panlabs Taiwan, LTD. These studies were part of the initial overall pharmacology and safety pharmacology assessment of MS-20 after single and long term treatment. Micro-Bio. Co., LTD does not consider these studies as official toxicity studies, nevertheless are presented here as reference material only.

F. Ames Assay

MS-20 was evaluated for their potential to induce reverse mutation at specific histidine loci in strains of salmonella typhimurium. Test article at concentrations of 5, 2.5, 1, 0.5 and 0.25 % did not cause significant increases in reversions when compare to the spontaneous reversions of the control.

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G. Acute Toxicity Study in ICR Mice

Test article were orally administered to 10/sex/group of ICR mice at dose levels of 0, 1, 20, 40 ml/kg body weights. The mice were observed for 14 days after treatment. Appearance observation, mortality, body weight, food consumption, visceral examination, clinical chemistry analysis and hematology analysis were performed for the study. All mice treated at 40 ml/kg body weights expired at 4 hours post treatment (assuming the deaths were caused by excessive dosing volume). Other treated mice did not exhibit any significant difference in parameters measured except the 20 ml/kg body weights group had slight muscle relax (i.e. abdominal tone, limb tone) within one hour after treatment.

H. Twenty-eight Days Oral Toxicity Study in ICR Mice

MS-20 was administered to 10/sex/group of ICR mice for 28 consecutive days at dose levels of 0, 1, 10, and 20 ml/kg body weights. Parameters observed or measured including mortality, appearance observation, body weight, food consumption, visceral examination, clinical chemistry analysis, and hematology analysis. All mice treated at 20 ml/kg body weights exhibited slight muscle relax (i.e. abdominal tone, limb tone, and grip strength) one hour after each treatment. All other parameters were comparable to the controls.

I. Long-Term (6 months) Study in General Pharmacology Screen

Male Wistar rats and male ICR mice were treated with MS-20 at 0.5 or 1.0 ml/kg body weights respectively for 6 months. The results indicated no abnormalities in behavior, automatic signs, organs, blood, body metabolism, heart rates, blood pressure, and body weights. No gross toxicity, mortality and tumorigenesis (pathological lesions) were observed as well. This study suggested that rats and mice given 5 to 10 times of the recommended human dose for dietary supplement products did not exhibit adverse effects.

Similar products using the same strains of beneficial microorganisms and culture conditions were produced in smaller scale and were sold in Japanese market through direct sale to hospitals for more than 50 years as a Nutrient

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Supplement. To our knowledge, there were no serious adverse effects reported either in mass media or in medical journal.

After careful assessment of all the information available including: the GMP manufacturing procedures; cGMP formulation facility; consistent quality products with well established product specifications and quality control procedures; complete battery of genetic toxicity studies with negative results; acute, subacute, and 6-month animal study at highest possible dose volume for animals which provide high margin of safety for human; long history of human use without adverse effects etc. MicroBio Co. LTD concluded that under the condition of labeling instructions, the dietary supplement product "NK Activator" containing MS-20 does not present significant or unreasonable risk of illness and injury, and will be reasonably expected to be safe.